

Idiopathic Relapsing Thrombotic Thrombocytopenic Purpura with Persistent ADAMTS13 Inhibitor Activity Treated Sequentially with Plasmapheresis, Rituximab, Cyclophosphamide and Splenectomy

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Key Words

ADAMTS13 · Idiopathic relapsing thrombotic thrombocytopenic purpura · Plasmapheresis · Rituximab

Abstract

We here describe a patient with an idiopathic thrombotic thrombocytopenic purpura (TTP) secondary to an ADAMTS13 inhibitor that continued to be dependent on plasmapheresis until the patient was treated with rituximab. TTP manifestations subsided with rituximab treatment in spite of a persistently low ADAMTS13 activity and continued a detectable inhibitor activity until the patient developed an intolerance to rituximab due to an allergic reaction when cyclophosphamide was added; this resulted in a normalization of ADAMTS13 activity and the disappearance of the inhibitor. Later, the patient developed an intolerance to rituximab due to a severe allergic reaction. Soon after stopping rituximab, the ADAMTS13 activity level dipped below 5% in addition to the appearance of the ADAMTS13 inhibitor. The patient had a splenectomy after rituximab and cyclophosphamide treatment; the medication was stopped based on several case reports of a complete remission of TTP after splenectomy. We believe that the reason TTP went into remission in our patient was because of rituximab treatment, in spite of both persistently low ADAMTS13 activity and a detectable inhibitor activity due to reducing the release of von Willebrand factor large multimers from the endothelial cells. We found that ADAMTS13 activity normalized and the inhibitor activity became undetectable when cyclophosphamide was added to rituximab. We suggest adding cyclo-

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phosphamide to rituximab for the treatment of patients with persistent ADAMTS13 inhibitors in order to prolong the remission period and lower the rate of relapse. © 2015 S. Karger AG, Basel

Introduction

Thrombotic thrombocytopenic purpura (TTP) is associated with a decrease in the activity of the von Willebrand factor-cleaving protease ADAMTS13. This decrease can be due to a congenital deficiency or the presence of an inhibitor. The treatment of TTP in the presence of an inhibitor is plasmapheresis to remove the inhibitor and to replenish ADAMTS13. We here describe a patient with an idiopathic TTP secondary to ADAMTS13 inhibitor that continued to be dependent on plasmapheresis until she was treated with rituximab. TTP manifestations subsided with rituximab treatment in spite of a persistently low ADAMTS13 activity and continued detectable inhibitor activity until the patient developed an intolerance to rituximab due to an allergic reaction when cyclophosphamide was added; this resulted in a normalization of her ADAMTS13 activity and the disappearance of the inhibitor.

Case Presentation

A 53-year-old African American woman with a past medical history of hypertension presented with abdominal pain, dizziness and confusion. At presentation, her platelet count was 14,000/mm³, lactate dehydrogenase 896 IU/l (normal value 98–192) and a peripheral smear showed increased schistocytes. She was diagnosed with TTP. Her ADAMTS13 activity was <5% (normal value >67%) and her inhibitor level was 0.5 inhibitor units (normal value <0.4 inhibitor units). She was treated with plasmapheresis and prednisone with an improvement in the platelet count, but she required ongoing plasmapheresis for several months with a failure to wean off her plasmapheresis. Her evaluation included a bone marrow biopsy, CT scans to rule out malignancy, an autoimmune and infectious workup – all were negative. She was later treated with rituximab 375 mg/m² weekly × 4 doses, and she was weaned off plasmapheresis. Rituximab was continued as a maintenance therapy initially every 3 months, and then every 6 months with a normal platelet count; however, ADAMTS13 activity remained <5%, accompanied with a high inhibitor level of up to 2 inhibitor units. Rituximab was stopped after 4 years of treatment. Seven months after rituximab stoppage, she presented with a TTP recurrence and a platelet count of 17,000/mm³. Rituximab was reintroduced; however, she started having allergic reactions even at a very low infusion rate and despite antihistamine and corticosteroid treatment. Cyclophosphamide as an immunosuppressant was added to rituximab at 1 g/m² every 3 months in a trial to lower the ADAMTS13 inhibitor titer. TTP went into remission once rituximab and cyclophosphamide were restarted, with a normalization of her platelet count. After 2 cycles of cyclophosphamide, the inhibitor and ADAMTS13 activity started to decrease, and by the fourth cyclophosphamide treatment, ADAMTS13 activity became normal at 67% with an undetected inhibitor level. Later, the patient developed an intolerance to rituximab due to a severe allergic reaction even at a very low infusion rate. Soon after stopping rituximab, ADAMTS13 activity levels dropped below 5% in addition to an appearance of ADAMTS13 inhibitors. The patient had a splenectomy after rituximab and cyclophosphamide treatment based on several case reports of a complete remission of TTP after splenectomy.

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Discussion

TTP is a life-threatening disease with a mortality rate of almost 90% if left untreated. It manifests as disseminated thrombotic microangiopathy, thrombocytopenia, hemolytic anemia, neurologic and renal dysfunction as well as fever [1–3].

TTP can be congenital or idiopathic, associated with anti-ADAMTS13 antibodies (autoimmune TTP), or secondary TTP associated with infection, pregnancy, and medications such as tacrolimus, mitomycin and cyclosporine A [4–8]. Congenital TTP is frequently associated with a severe ADAMTS13 deficiency.

TTP patients with ADAMTS13 inhibitors respond to plasma exchange although they frequently continue to have low ADAMTS13 activity and a detectable inhibitor while in remission [9]. A relapse of these patients often happens with conditions associated with an increased release of large von Willebrand multimers such as stress, infection, autoimmune diseases or pregnancy. This is also the case of congenital ADAMTS13 deficiency that can be accompanied with a prolonged period of remission with relapse usually associated with infections, surgery, pregnancy, or any type of stress [10]. Immunosuppression with corticosteroids, cyclophosphamide, vincristine, cyclosporine A, azathioprine, and splenectomy have been used to limit the production of autoantibodies with variable results [11]. Rituximab is a humanized monoclonal antibody against the B-cell antigen CD20 and is widely used in the treatment of B-cell lymphoproliferative disorders and several autoimmune diseases [12]. Rituximab has been reported to be effective in the treatment of TTP that is ADAMTS13 autoantibody-associated and refractory to therapy [10–12].

It is known that an ADAMTS13 activity value over 5–10% is sufficient to protect from disease recurrence [15]. Rituximab treatment results in a progressive disappearance of inhibitors with a subsequent increase in protease activity along with a normalization of von Willebrand factor pattern. The partial recovery of B cells after the discontinuation of rituximab is followed by a decline in ADAMTS13 activity and a reappearance of the inhibitor. The presence of ADAMTS13 inhibitors during remission have been reported in 30–40% of patients with recurrent TTP which is similar to our case [13]. However, the presence of ADAMTS13 inhibitors may pose a risk of relapse, and maintenance treatment with rituximab may be effective in maintaining a long-term relapse-free condition in patients with a diagnosis of chronic relapsing TTP and persistent ADAMTS13 inhibitor activity [14].

We believe that the reason TTP went into remission in our patient with rituximab treatment, in spite of both persistently low ADAMTS13 activity and detectable inhibitor activity, was due to reducing the release of von Willebrand factor large multimers from the endothelial cells. We found that ADAMTS13 activity normalized and the inhibitor activity became undetectable when cyclophosphamide was added to rituximab. We suggest adding cyclophosphamide to rituximab for the treatment of patients with persistent ADAMTS13 inhibitors in order to potentially prolong the remission period and lower the rate of relapse.

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